CHRONIC TOXICITY SUMMARY

CADMIUM AND CADMIUM COMPOUNDS

CAS Registry Number: 7440-43-9

I.   Chronic Toxicity Summary

Inhalation reference exposure level	**0.02 ㎍/m³** (respirable)
Critical effect(s)	Kidney effects (proteinuria) and respiratory effects (reduction in forced vital capacity and reduction in peak expiratory flow rate) in occupationally exposed humans
Hazard index target(s)	Kidney; respiratory system

II.   Physical and Chemical Properties (ATSDR, 1993)

Description	Blue-white solid
Molecular formula	Cd
Molecular weight	112.41 g/mol
Density	8.642 g/cm³ @ 20ºC
Boiling point	765ºC (CRC, 1994)
Melting point	320.9ºC
Vapor pressure	1 torr @ 394ºC
Conversion factor	Not applicable

III.   Major Uses or Sources

The production of nickel-cadmium batteries is currently the primary use of cadmium (ATSDR, 1993). Cadmium, a by-product of zinc- and sulfide-ore processing, is also used for metal plating and in pigments and plastics. The annual statewide industrial emissions from facilities reporting under the Air Toxics Hot Spots Act in California based on the most recent inventory were estimated to be 3672 pounds of cadmium (CARB, 2000).

IV.   Effects of Human Exposure

Pulmonary and renal function were examined in three worker groups: women with less than 20 years of exposure [group E1]; men with less than 20 years of exposure [group E2], and men with more than 20 years of exposure [group E3] (Lauwerys *et al.*, 1974). Exposed groups were matched to control groups in terms of age, body size, cigarettes smoked per day, duration of smoking, and duration of employment. Although urine cadmium concentrations were significantly elevated, the subjects in E1 did not exhibit pulmonary function changes or

proteinuria indicative of renal impairment. The workers in E1 had been exposed for a mean of 4.08 years to 31 µg/m³ total cadmium (1.4 µg/m³ respirable cadmium). The 27 workers in E2 had been exposed for a mean of 8.6 years to 134 µg/m³ total cadmium (88 µg/m³ respirable cadmium). The blood and urinary cadmium levels of these workers were also significantly elevated compared to matched controls. Glomerular proteinuria was observed in 15% of the workers in E2 and in 68% of workers in E3. The 22 workers of E3 had been exposed for a mean of 27.8 years to 66 µg/m³ total cadmium (21 µg/m³ respirable cadmium). Significantly increased levels of cadmium were observed in the blood and urine, and workers in E3 also exhibited significant decreases in some measures of pulmonary function (forced vital capacity, forced expiratory volume in one second, and peak expiratory flow rate). This study identifies the kidney as the key target organ of chronic cadmium exposure. For respirable cadmium, this study indicates a LOAEL of 21 µg/m³ for workers exposed for 28 years and a NOAEL of 1.4 µg/m³ for workers exposed for 4 years.

A study of 82 cadmium exposed workers reports the time-weighted cumulative exposure index (TWE) and cadmium body burden determined in vivo (Ellis *et al.*, 1985). Evidence of renal dysfunction (usually elevated urinary β_2-microglobulin) was consistently observed when the worker's liver cadmium burden exceeded 40 ppm and the time-weighted cumulative exposure index exceeded 400-500 µg years/m³.

A detailed investigation of renal function in 75 male cadmium-exposed workers identified significant increases in urinary excretion of several low- and high molecular weight proteins, including β_2-microglobulin, and significant decreases in renal reabsorption of calcium, urate, and phosphate compared to controls (Mason *et al.*, 1988). Exposures, which ranged from 36 to 600 µg/m³, were determined from background or personal exposure measurements made between 1964 and 1983, or were estimated. A time-weighted cumulative exposure index (TWE) was determined for each subject. A two phase linear regression model was applied to the data to identify inflection points for each biochemical parameter. The biochemical indicators most highly correlated to exposure were urinary retinol binding protein and urinary β_2-microglobulin. Of these, the most sensitive parameter, urinary β_2-microglobulin, demonstrated an inflection point at 1108 µg years/m³ with a 95% lower confidence limit of 509 µg years/m³. The endpoint selected is indicative of defects in tubular reabsorption of proteins.

Diminished sensitivity of smell has also been observed in cadmium exposed workers (Rose *et al.*, 1992). Cadmium body burden, β_2-microglobulin levels, and olfactory function were measured in a group of 55 male workers exposed to cadmium fumes in a brazing operation. A group of 15 control workers was also tested. Exposed workers exhibited high urinary cadmium levels, tubular proteinuria, and a significant, selective defect in odor detection threshold.

V.   Effects of Animal Exposure

Interstitial infiltration of lymphocytes and leukocytes and hyaline casts were observed in the kidneys of rabbits following exposure to 6.5 mg/m³ cadmium-iron dust for 3 hours per day, 21 days per month for 9 months (Friberg, 1950). Proteinuria was observed in the majority of exposed rabbits by the fourth month of exposure. Increased lung weights and emphysema were

also observed. The trachea and nasal mucous membranes exhibited chronic inflammatory changes (not specified) and lymphocyte infiltration. The kidney contained the greatest concentration of cadmium. This study also exposed a group of rabbits to 9.1 mg/m^3 cadmium-iron dust for 3 hours per day, 23 days per month, for 7 months. Two rabbits in this group died from acute pneumonia at one month, and one rabbit was terminated at 3 months of exposure. Findings at necropsy were similar, although more severe than those observed in rabbits exposed to 6.5 mg/m^3. Chronic bronchitis and hyperplasia of the bronchiolar epithelium were observed in the higher dose group in addition to the findings previously noted.

Male and female rats were exposed to 0, 0.3, 1.0, or 2.0 mg Cd/m^3 (as CdCl$_2$) 6 hours per day, 5 days per week for a total of 62 exposures (Kutzman *et al.*, 1986). Rapid, shallow breathing and marked weight loss were observed in the highest dose group; all animals in this group died within the first 45 days of exposure. A dose-dependent increase in lung weight was observed in the remaining dose groups and a statistically significant increase in lung collagen and elastin was observed in rats exposed to 1.0 mg/m^3. Pathological changes noted in the terminal bronchioles include flattening and hyperplasia of type II cells, and infiltration of macrophages, mononuclear cells, and polymorphonuclear leukocytes. Proliferation of fibroblasts with deposition of collagen was also noted.

Male rats were exposed continuously to 0, 30, or 90 µg Cd/m^3 cadmium oxide (CdO) dust for up to 18 months (Takenaka *et al.*, 1990). Animals exposed to 30 µg/m^3 were sacrificed at 6 and 18 months of exposure. Although some rats in the high dose group were terminated after 6 months of exposure, the remaining rats were terminated after 7 months due to increased mortality and were not included in the study. Inflammation and hyperplasia of the alveolar epithelium occurred in animals of both groups after 6 months of exposure with more marked changes observed in the high dose group. Abnormal proliferation of the epithelium was observed in the low dose group following 18 months of exposure. Lung tumors observed in both dose groups were characterized as being duration dependent.

VI. Derivation of Chronic Reference Exposure Levels (REL)

Derivation of Chronic Inhalation Reference Exposure Level

Study	Lauwerys *et al.*, 1974
Study population	Humans (22 exposed men and 22 unexposed men in LOAEL group; 31 exposed women and 31 non-exposed women in NOAEL group)
Exposure method	Occupational exposures
Critical effects	Kidney effects - proteinuria in 68% of LOAEL group
	Respiratory effects – reduction in forced vital capacity (FVC), forced expiratory flow in 1 second (FEV$_1$); reduction in peak expiratory flow rate
LOAEL	21 µg/m^3 respirable cadmium
NOAEL	1.4 µg/m^3 respirable cadmium
Exposure continuity	Assumed to be 5 days/week for 8 hours/day during which 10 m^3 air is breathed
Average occupational exposure	0.5 µg/m^3 for NOAEL group (1.4 x 10/20 x 5/7)
Human equivalent concentration	0.5 µg/m^3 for NOAEL group
Exposure duration	Average of 4.1 years (1 to 12 years) for NOAEL group
LOAEL uncertainty factor	1
Subchronic uncertainty factor	3
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	30
Inhalation reference exposure level	0.02 µg/m^3

VII. Data Strengths and Limitations for Development of the REL

This evaluation of a chronic REL for cadmium is strengthened by being based on a human exposure study of workers exposed to cadmium for periods of 1 to over 20 years. The exposed group was matched to a control group in terms of age, body size, cigarettes smoked per day, duration of smoking, and duration of employment. The factory process was unchanged over the study period suggesting that exposures may have remained relatively constant over time. Significant areas of uncertainty include an incomplete knowledge of the past exposures over the full study interval and the relatively small number of subjects in the study.

A similar evaluation of the LOAEL group led to an alternate estimate for an inhalation reference exposure level of 0.05 µg/m^3. The LOAEL group had an average occupational exposure of 5.0 µg/m^3 and an average exposure duration of 27.8 years (21 to 40 years). Default uncertainty

factors included a 10-fold LOAEL uncertainty factor and a 10-fold intraspecies uncertainty factor (UF).

For comparison, using data presented by Ellis and associates (1985) and Mason and associates (1993) correlating human cumulative exposures (in terms of μg-years/m^3) and renal tubular protein reabsorption, a LOAEL of 500 μg-years/m^3 was predicted. This correlates to 7 μg/m^3 over 70 years. A time-weighted exposure to account for continuous exposure rather than 40 hour per week occupational exposure is 1.7 μg/m^3. Applying a 10-fold LOAEL uncertainty factor and a 10-fold intraspecies uncertainty factor results in a REL value of 0.02 μg/m^3, the same value obtained using the Lauwerys *et al*. data. U.S. EPA has not published an RfC for cadmium.

In addition to being inhaled, airborne cadmium can settle onto crops and soil and enter the body by ingestion. Thus an oral chronic reference exposure level for cadmium is also required. We propose adopting the U.S. EPA RfD as the chronic oral REL.

Derivation of Chronic Oral Reference Exposure Level (U.S. EPA RfD)

Study	U.S. EPA, 1985
Study population	Humans
Exposure method	Food and drinking water
Critical effects	Significant proteinuria
LOAEL	Not observed
NOAEL	0.005 mg/kg bw-day
Exposure continuity	Chronic
Exposure duration	Up to lifetime
Average exposure	0.005 mg/kg bw-day
LOAEL uncertainty factor	1
Subchronic uncertainty factor	1
Interspecies uncertainty factor	1
Intraspecies factor	10
Cumulative uncertainty factor	10
Oral reference exposure level	0.0005 mg/kg bw-day

The oral REL is the U.S. EPA's Reference Dose (RfD) (U.S. EPA, 1996). A concentration of 200 μg cadmium (Cd)/gm wet human renal cortex is the highest renal level not associated with significant proteinuria (U.S. EPA, 1985). A toxicokinetic model is available to determine the level of chronic human oral exposure (NOAEL) which results in 200 μg Cd/gm wet weight human renal cortex. The model assumes that 0.01% of the Cd body burden is eliminated per day (U.S. EPA, 1985). Assuming 2.5% absorption of Cd from food or 5% from water, the toxicokinetic model predicts that the NOAEL for chronic Cd exposure is 0.005 and 0.01 mg Cd/kg/day from water and food, respectively (i.e., levels which would result in 200 μg Cd/gm wet weight human renal cortex). Thus, based on an estimated NOAEL of 0.005 mg Cd/kg/day for Cd in drinking water and an UF of 10, an RfD of 0.0005 mg Cd/kg/day (water) was calculated; an equivalent RfD for Cd in food is 0.001 mg Cd/kg/day.

Cd is unusual in relation to most, if not all, of the substances for which an oral RfD has been determined in that a vast quantity of both human and animal toxicity data are available. The RfD is based on the highest level of Cd in the human renal cortex (i.e., the critical level) not associated with significant proteinuria (i.e., the critical effect). A toxicokinetic model has been used to determine the highest level of exposure associated with the lack of a critical effect. Since the fraction of ingested Cd that is absorbed appears to vary with the source (e.g., food vs. drinking water), it is necessary to allow for this difference in absorption when using the toxicokinetic model to determine an RfD.

The uncertainty factor of 10 is used to account for intrahuman variability to the toxicity of this chemical in the absence of specific data on sensitive individuals. No modifying factor was used.

U.S. EPA stated its confidence in the RfD as: Study - Not applicable; Data Base - High; and RfD – High. The choice of NOAEL does not reflect the information from any single study. Rather, it reflects the data obtained from many studies on the toxicity of cadmium in both humans and animals. These data also permit calculation of pharmacokinetic parameters of cadmium including absorption, distribution, metabolism, and elimination. All this information considered together gives high confidence in the data base. High confidence in the RfD follows as well.

VIII.   References

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